Clinical Trials

Translational Research : Bench to bedside, Clinical Trials

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Disclosures

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1. Dr. Smith is a co-inventor on 10 patents – some related to pancreatic cancer.
2. Dr. Smith is the Director of Clinical & Translation Research, LLC, a biotech research consulting company
   - Consultant for Immune Therapeutics, Cytocom, and Cato Research, Inc.

OBJECTIVES

- Understand how an idea is taken from the research lab to patient care.
- Learn the steps in conducting clinical trials
- Comprehend some of the obstacles to overcome in drug development?
- Examples of my translational projects
- Pitfalls and the Prize

Research and Drug Development

Research & Drug Development

Preclinical research

Bottleneck of Drug development

Drug development

An Overview of the Drug Development Process

Preclinical	Clinical				Approval	Market
Toxicology	Investigational New Drug Application	Phase I	Phase II	Phase III	New Drug Application	Phase IV / Postmarket surveillance
		safety	safety dosing efficacy	safety efficacy side effects		
Expenses		$15.2 million	$23.4 million	$86.5 million		
Time		21.6 months	25.7 months	30.5 months		
1 to 6 years	6 to 11 years				0.6 to 2 years	11 to 14 years
Overall probability of success						
		30%	14%	9%	8%	
Conditional probability of success						
	40%	75%	48%	64%	90%	
Sources: Dimasi, Hansen, and Grabowski (2003).						
Notes: The line marked "Overall probability of success" is the unconditional probability of reaching a given stage. For example, 30 percent of drugs make it to phase I testing. The line marked "Conditional probability of success" shows the probability of advancing to the next stage of the process conditional on reaching a given stage. For example, the probability of advancing to Phase III testing conditional on starting Phase II testing is 48 percent.						

Drug development

Drug Development

- In the United States, it takes an average of 12 years for an experimental drug to travel from the laboratory to your medicine cabinet.
- Only 5 in 5,000 drugs that enter preclinical testing progress to human testing. One of these 5 drugs that are tested in people is approved. The chance for a new drug to actually make it to market is thus only 1 in 5,000.
- The process of drug approval is controlled in most countries by a governmental regulatory agency. In the U.S., the Food and Drug Administration (FDA) governs this process. The FDA requires the following sequence of events before approving a drug.

Preclinical Testing:
Investigational New Drug Application (IND
Phase I Clinical Trials
Phase II Clinical Trials:
Phase III Clinical Trials:
New Drug Application (NDA):
Phase IV Studies
Although there are other routes that can expedite the process (referred to as fast-tracking

Preclinical studies

Preclinical Studies

Preclinical Testing: research lab conducts certain studies before the future drug is ever given to a human being. Laboratory and animal studies must be done to demonstrate the biological activity of the drug against the targeted disease. The drug must also be evaluated for safety. These tests take on the average 3 1/2 years.

Phase 1

Phase 1

- 15-30 people
- Determines
  - what dose is safe?
  - How the treatment should given?
  - Pharmacokinetics?
  - How the treatment affects the body?
  - Safety & toxicity

How much?

What route of administration?

Phase 2

Phase 2: Efficacy

- Less than 100 people
- Must have a primary endpoint
- Usually unbiased (blinded)
- Determines
  - Does it work?
  - Is it more effective than a placebo?
  - Does not compare with other treatments

Phase 3

Phase 3

- From 100 to thousands of people
- Equal chance to be assigned to one of two or more groups
- Determines
  - How the new treatment compares with the current standard
  - Or how it compares with placebo
  - Superiority or non-inferiority trials

Phase 4

Phase 4

- From hundreds to thousands of people
- Usually takes place after drug is approved to provide additional information on the drug's risks, benefits and optimal use
- Called 'Post-marketing" or

Or post-approval trials

Pilot Study

Pilot Study

- A small study that helps develop a bigger study
- A first venture into a particular area
- Used to iron out possible difficulties, and help with design of the bigger, more pivotal study.
- Helps provide ‘tentative response rate’ to estimate the sample size needed in a Phase 2 trial to reach significance over control

Randomized clinical trials

Randomized Clinical Trials

- Equal chance to be assigned to one of two or more groups
  - One group gets the most widely accepted treatment (standard treatment) or placebo
  - The other gets the new treatment being tested
- All groups are as similar as possible
- Provides the best way to prove the effectiveness of a new agent or intervention

Patient rights

How Are Patients' Rights Protected?

- Ethical and legal codes that govern medical practice also apply to clinical trials
- Informed consent
- Review boards
  - Scientific review
  - Institutional review boards (IRBs)
  - Data safety and monitoring boards

Genetic testing
Add to consent

IND

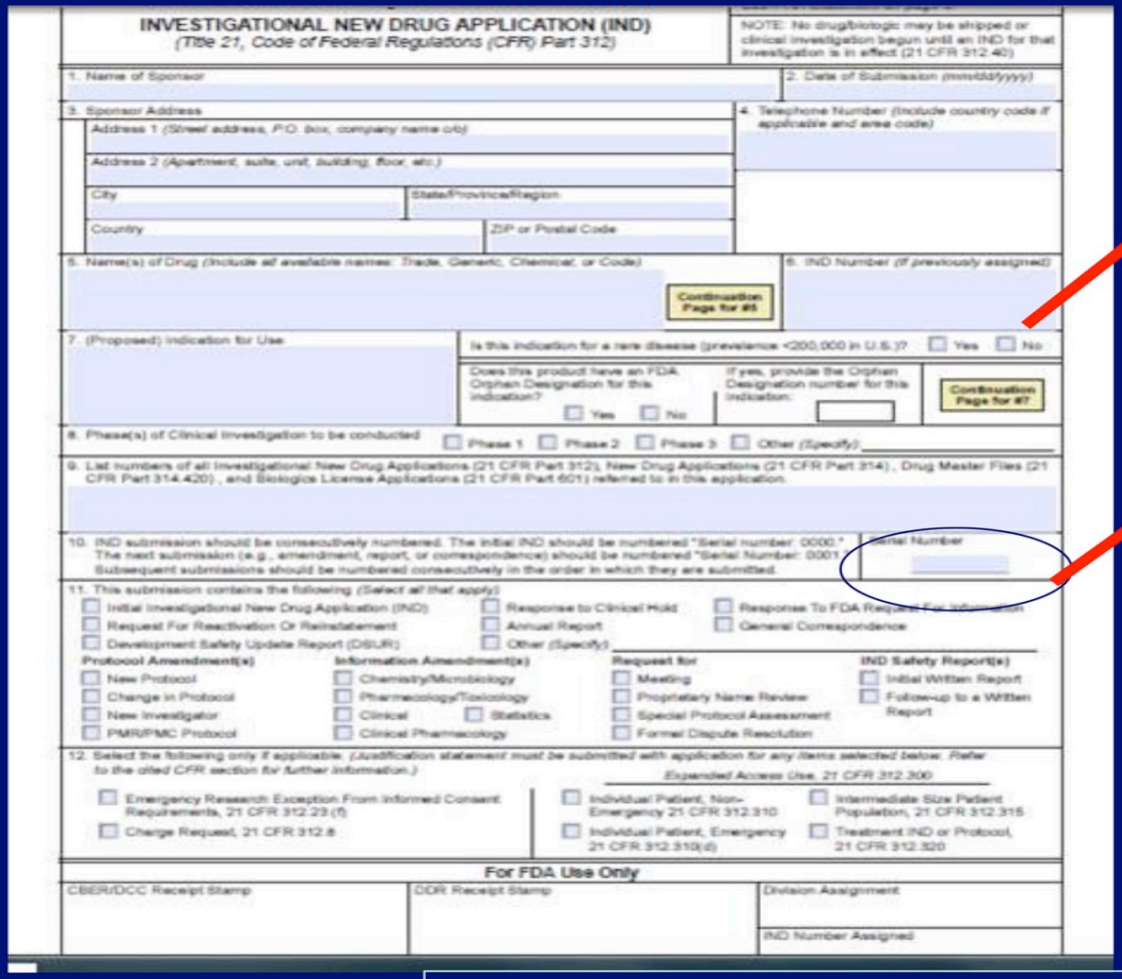
Investigational New Drug (IND) Application

- **Need approval from FDA**
  - **Apply for and IND# (investigational new drug#)**
  - **1571 and 1572**

The IND becomes effective if the FDA does not disapprove it within 30 days.
The IND must include the following information: the results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. The IND must also be reviewed and approved by the Institutional Review Board where the studies will be conducted.

FDA forms

FDA 1571 and 1572 forms, info about sponsor & drug



INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
2. Date of Submission (mm/dd/yyyy)
3. Sponsor Address
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City
State/Province/Region
Country
ZIP or Postal Code
4. Telephone Number (Include country code if applicable and area code)
5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code)
Continuation Page for #5
6. IND Number (If previously assigned)
7. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes No
Does this product have an FDA Orphan Designation for this indication? Yes No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
8. Phase(s) of Clinical Investigation to be conducted Phase 1 Phase 2 Phase 3 Other (Specify):
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314), Drug Master Files (21 CFR Part 314.420), and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.
Serial Number
11. This submission contains the following (Select all that apply)
Initial Investigational New Drug Application (IND)
Request For Reactivation Or Reinstatement
Development Safety Update Report (DSUR)
Response to Clinical Hold
Annual Report
Other (Specify)
Response To FDA Request For Information
General Correspondence
Protocol Amendment(s): New Protocol; Change in Protocol; New Investigator; PMR/PMC Protocol
Information Amendment(s): Chemistry/Microbiology; Pharmacology/Toxicology; Clinical; Statistics; Clinical Pharmacology
Request for: Meeting; Proprietary Name Review; Special Protocol Assessment; Formal Dispute Resolution
IND Safety Report(s): Initial Written Report; Follow-up to a Written Report
12. Select the following only if applicable. (Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)
Expanded Access Use, 21 CFR 312.300
Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
Charge Request, 21 CFR 312.8
Individual Patient, Non-Emergency 21 CFR 312.310
Individual Patient, Emergency 21 CFR 312.310(d)
Intermediate Size Patient Population, 21 CFR 312.315
Treatment IND or Protocol, 21 CFR 312.320
For FDA Use Only
CBER/DCC Receipt Stamp
DDR Receipt Stamp
Division Assignment
IND Number Assigned

6. IND Number *(If previously assigned)*

050987

Serial Number

0001

What are you Submitting or requesting In this report

Must be submitted with <u>every</u> communication to FDA

Intellectual Property

Intellectual Property

- Submit an invention disclosure and provisional patent before you present the research results publically (including abstracts).
- The patent belongs to whomever you worked for when you made the discovery. If your employer does not want to file a patent have them assign the rights to you.

Clinical trials

Other things to do for a Clinical Trial

- Write a protocol- study design with outcomes
- Write a consent form
- Obtain IRB approval
- Find a Sponsor - Get Funding support-$
- Responsibilities of the Principal Investigator (CITI training)
- Research Nurse /Study coordinator
- Registration of clinical trial on www.clinicaltrials.gov

Phase 1

Phase 1: first in human trial

- Study the safety and toxicity of drug in humans
- Determine the Maximum-Tolerated Dose (MTD)
- Study the biological kinetics and metabolism of OGF (Pharmacokinetics)
- Study the route of administration

25g → 70kg

Calculating human dose

Calculating human dose from animal study

Nair AB, Jacob S. Journal of Basic and Clinical Pharmacy. 2016;7(2):27-31.

Species	Reference body weight (kg)	Working weight range (kg)	Body surface area (m^2)	To convert dose in mg/kg to dose in mg/m^2, multiply by K_m	To convert animal dose in mg/kg to HED in mg/kg, either	
					Divide animal dose by	Multiply animal dose by
Human	60	-	1.62	37	-	-
Mouse	0.02	0.011-0.034	0.007	3	12.3	0.081
Hamster	0.08	0.047-0.157	0.016	5	7.4	0.135
Rat	0.15	0.08-0.27	0.025	6	6.2	0.162
Ferret	0.30	0.16-0.54	0.043	7	5.3	0.189
Guinea pig	0.40	0.208-0.700	0.05	8	4.6	0.216
Rabbit	1.8	0.90-3.0	0.15	12	3.1	0.324
Dog	10	5-17	0.50	20	1.8	0.541
Monkeys (rhesus)	3	1.4-4.9	0.25	12	3.1	0.324
Marmoset	0.35	0.14-0.72	0.06	6	6.2	0.162
Squirrel monkey	0.60	0.29-0.97	0.09	7	5.3	0.189
Baboon	12	7-23	0.60	20	1.8	0.541
Micro pig	20	10-33	0.74	27	1.4	0.730
Mini pig	40	25-64	1.14	35	1.1	0.946

*Data obtained from FDA draft guidelines.[7] FDA: Food and Drug Administration, HED: Human equivalent dose

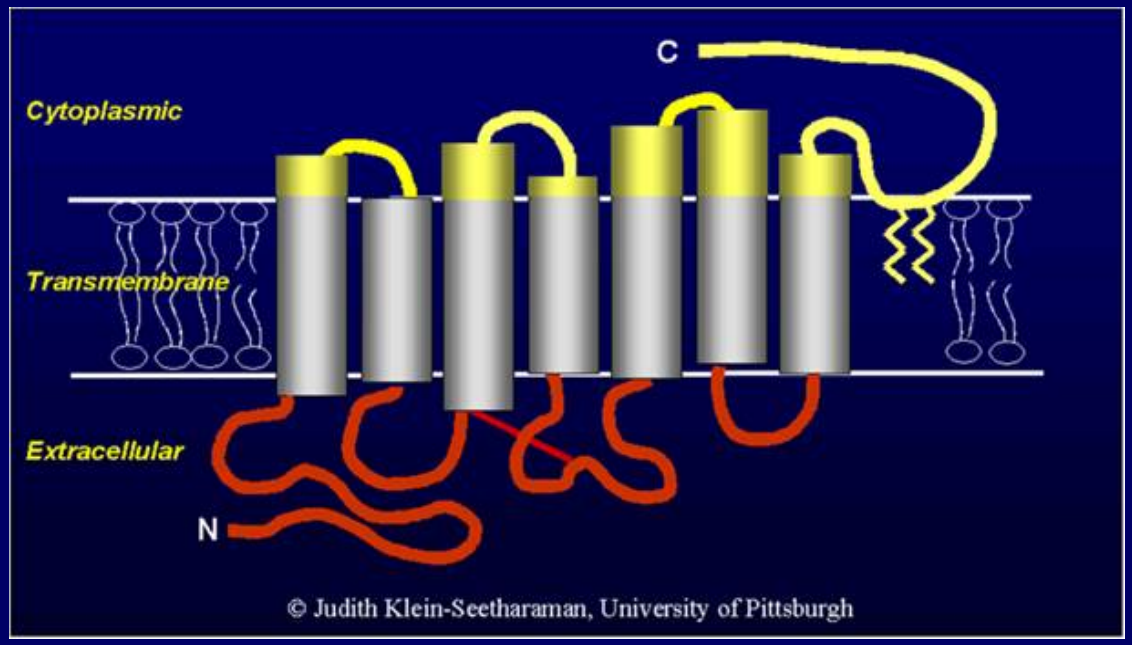
The dose by factor method applies an exponent for body surface area (0.67), which account for difference in metabolic rate, to convert doses between animals and humans. Thus, HED is determined by the equation:

$$HED\ (mg/kg) = \text{Animal NOAEL mg/kg} \times (\text{Weight}_{animal}\ [kg]/\text{Weight}_{human}\ [kg])^{(1-0.67)}$$

[no observed adverse effect levels (NOAEL) from preclinical research]

Cholecystokinin Receptors:

- GPCR: G-protein coupled receptors
- **7-trans-**
  - membrane
  - domains
- **Ligands:**
  - CCK and
  - **gastrin**



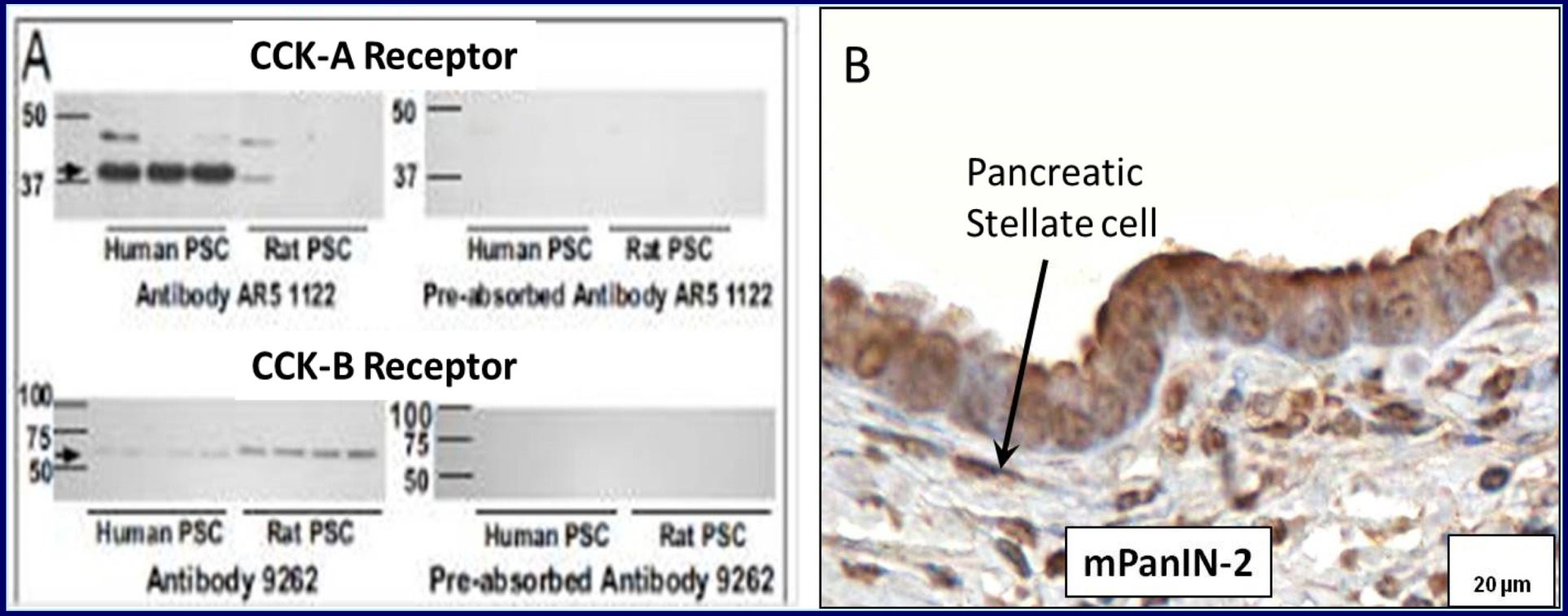
Cholecystokinin Receptors:

- CCK-A: alimentary tract, gallbladder, mouse pancreas. Binds CCK > Gastrin (1,000:1)

- CCK-B: brain, stomach, human pancreas
  - Binds CCK = Gastrin (1:1)

- CCK-C: pancreatic cancer, splice variant of CCK-B; Only found in human cancer, not rodents. Binds Gastrin > CCK (10:1)

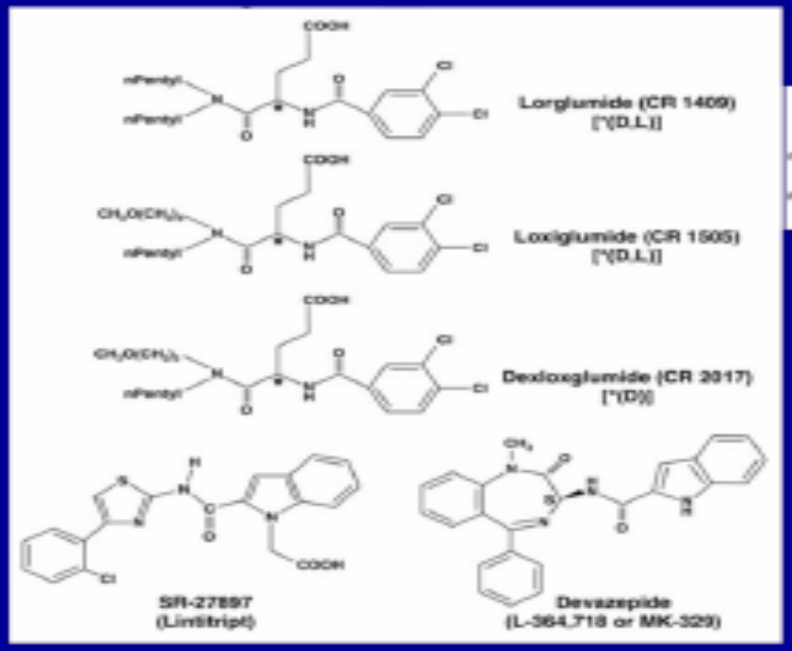
CCK Receptors are also on Pancreatic Stellate Cells



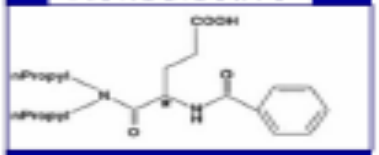
CCK receptor antagonists

CCK Receptor antagonists

CCK- A Antagonists

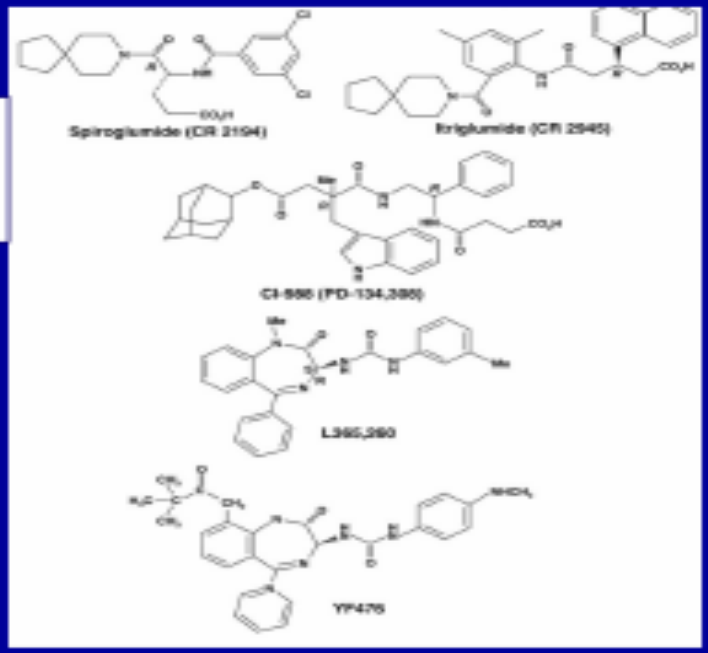


Proglumide Nonselective



Orally Bioavailable Previously tested in humans and deemed safe.

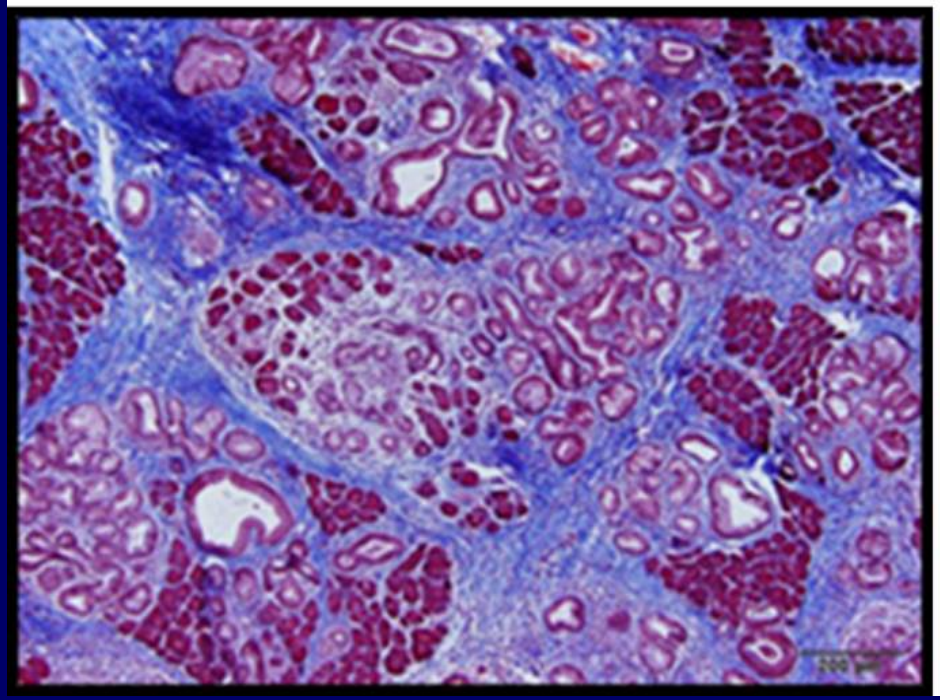
CCK-B antagonists



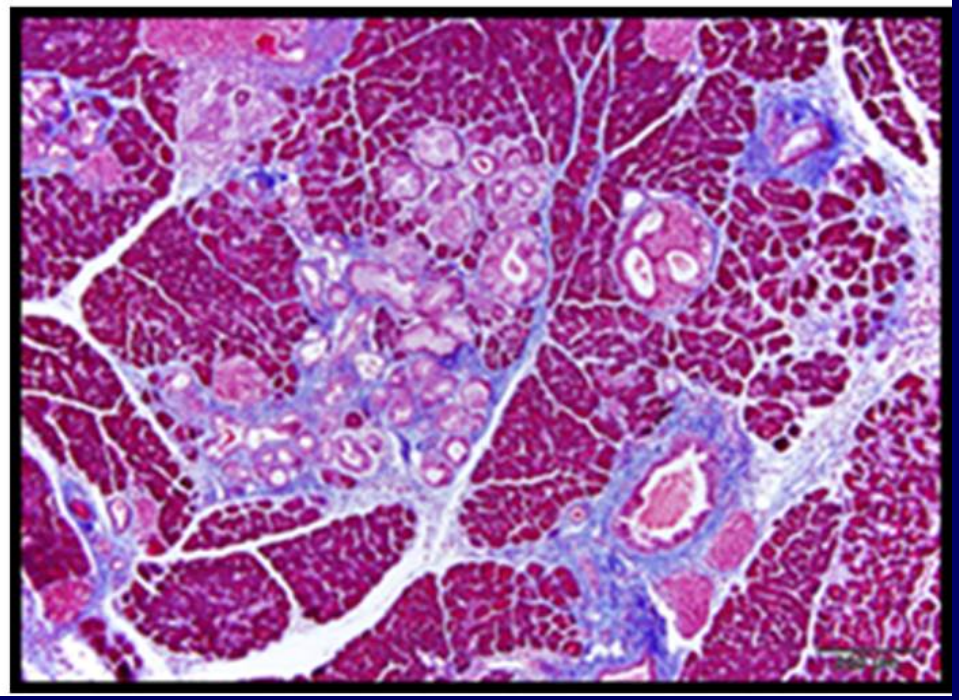
Berna and Jenson, *Curr Top Med Chem*. 2007

CCK Receptor Blockade Prevents Fibrosis in KRAS mouse

Vehicle control

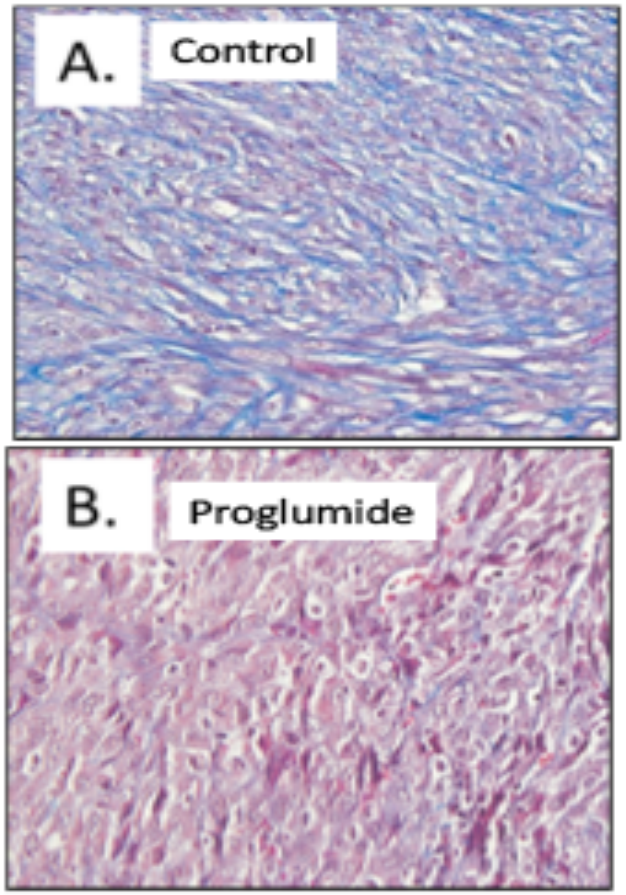


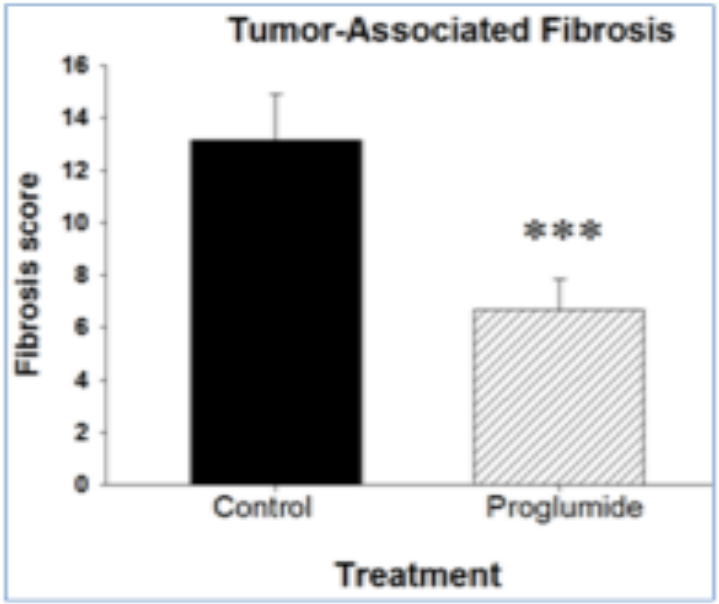
CCK receptor Blockade



CCK receptor antagonist

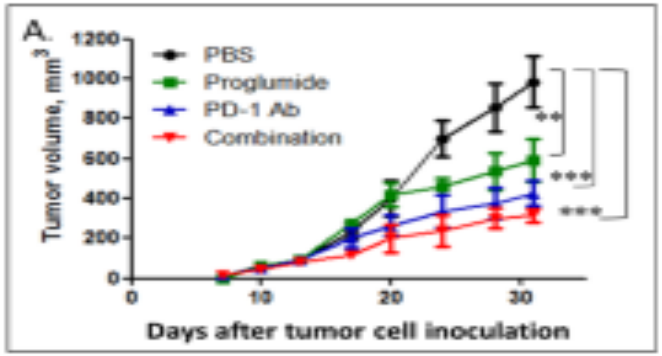
CCK Receptor Antagonist Reverse Fibrosis in Established SC pancreatic cancers

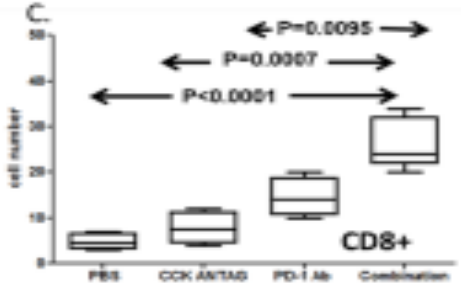


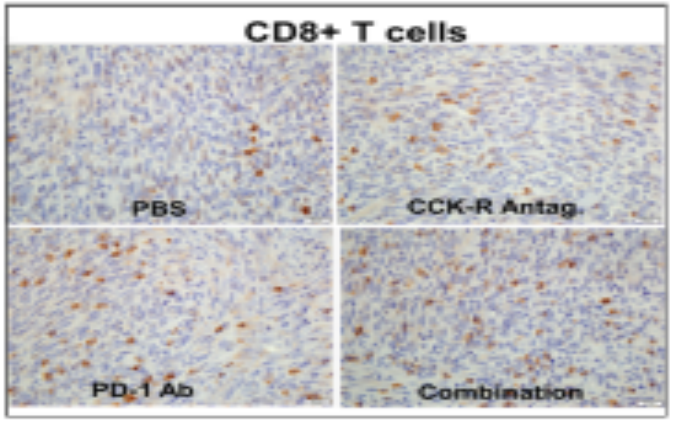


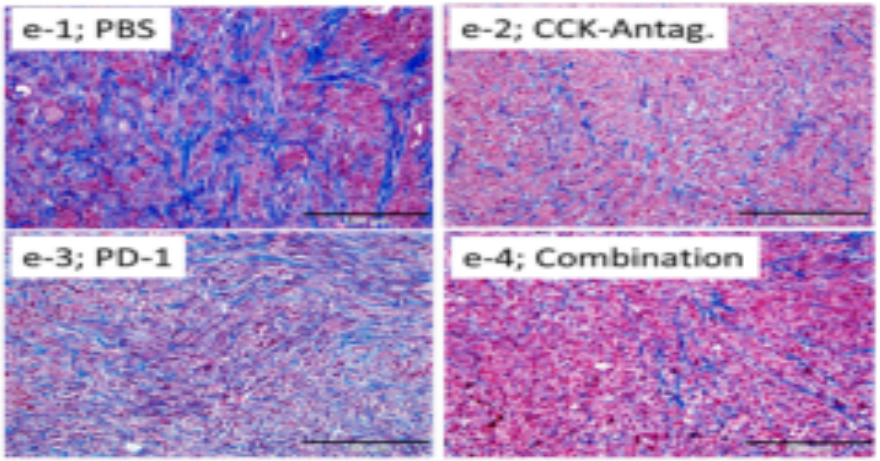
CCK receptor antagonist

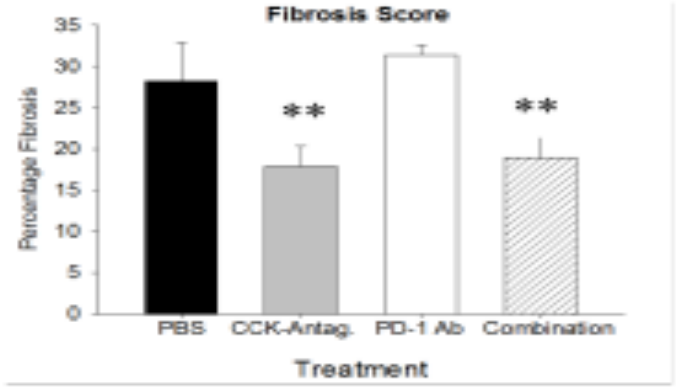
CCK Receptor antagonist decreases tumor fibrosis
Allowing for influx of CD8+ and improves PD-1 Ab







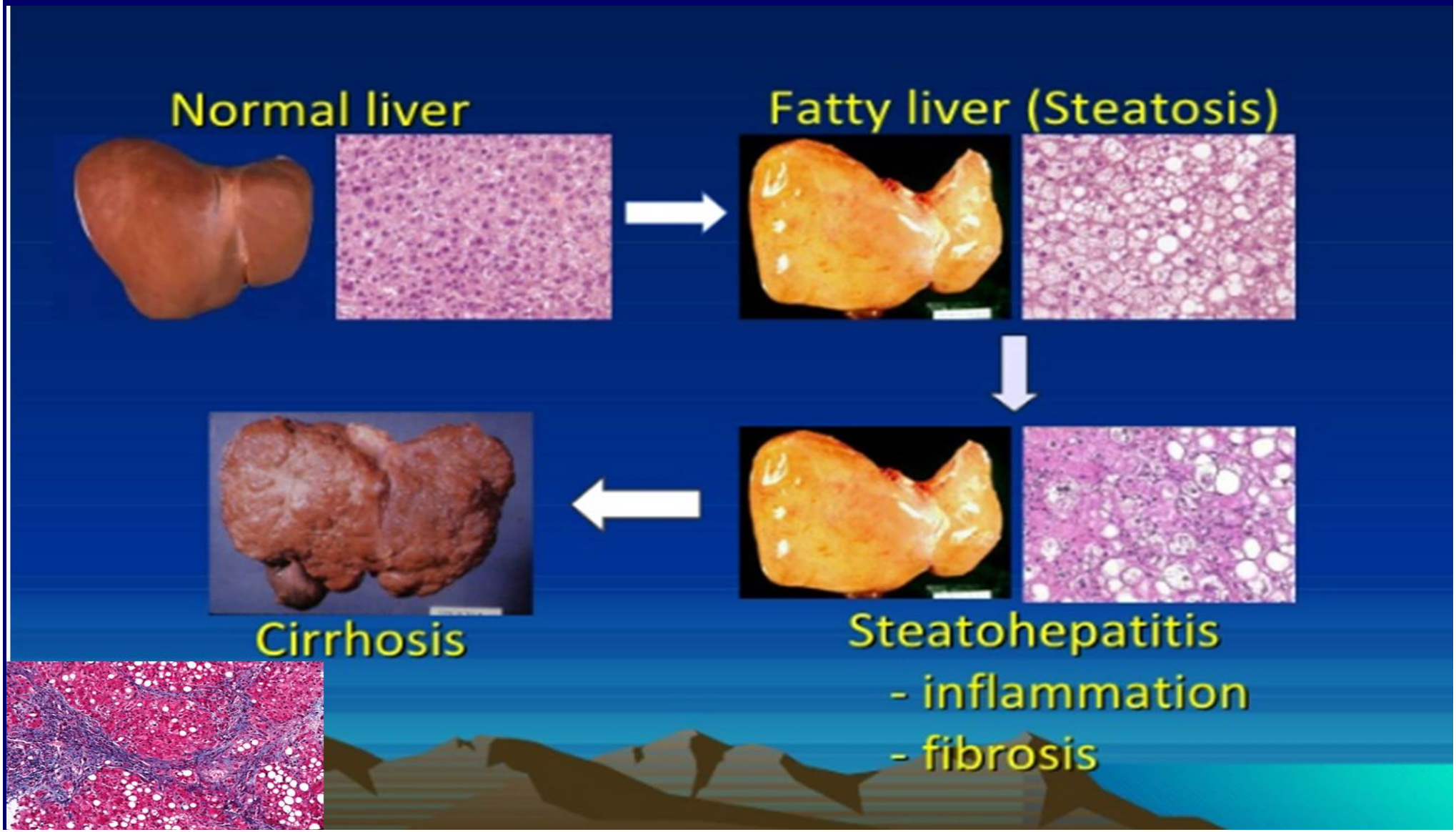




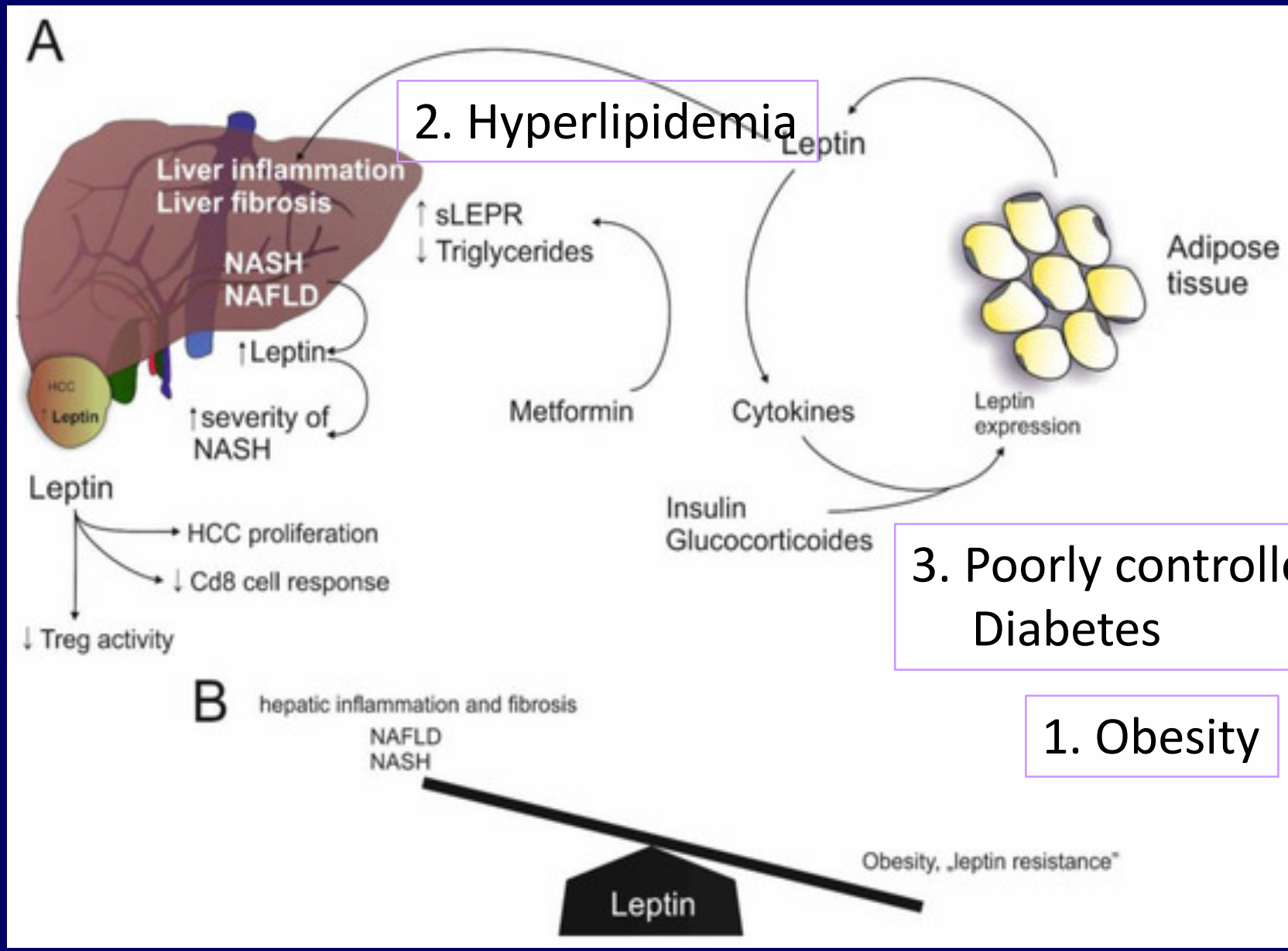
Non-Alcoholic Fatty Liver Disease (NAFLD)
Non-Alcoholic Steato-Hepatitis (NASH)

- An epidemic of the new Millennium
- A new consequence of the obesity epidemic
- Represents a spectrum of conditions characterized by steatosis in the absence of alcohol intake
- Histology:
  - Simple steatosis without inflammation
  - Steatohepatitis (NASH) with inflammation, fibrosis & cirrhosis

Liver cirrhosis



3 major causes of NAFLD /NASH



2. Hyperlipidemia

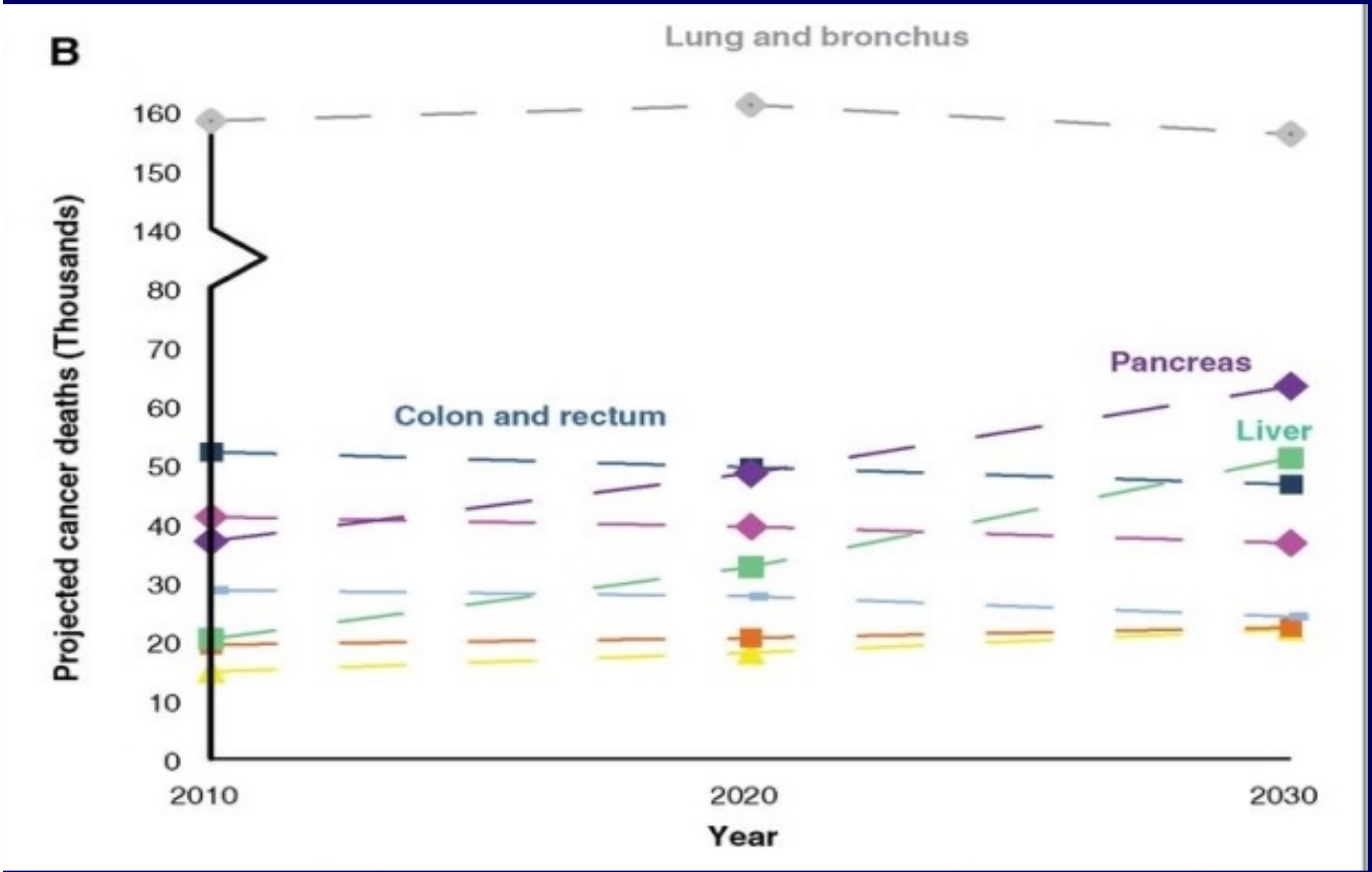
3. Poorly controlled Diabetes

1. Obesity

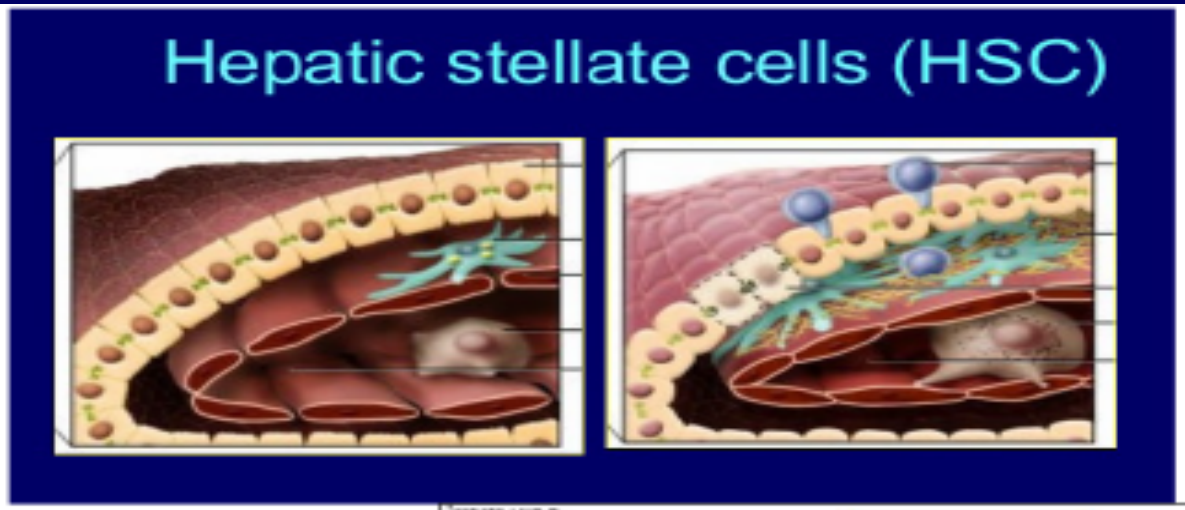
Treatment

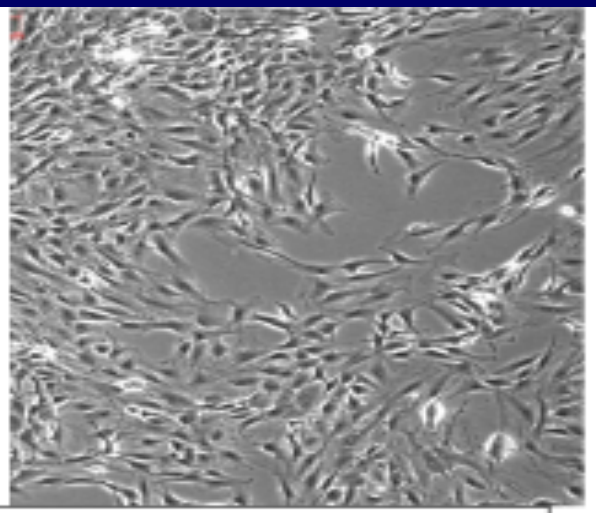
- Weight reduction
  - Orlistat- a gut lipase inhibitor to decrease fat absorption
- Diabetes management
  - Metformin is the preferred drug
  - GLP-1 drugs (not recommended –pancreatitis)
- Lipid lowering agents
  - Statins are not contraindicated
  - PPARα is the main target of fibrate drugs: gemfibrazole
- Antioxidants
  - Vitamin E 400-800 IU
- Peroxisome proliferator-activator receptors (PPARγs) agonists
  - Thiazolidinediones- Pioglitazone
- Others
  - Angiotensin converting enzyme inhibitors

Projected cancer deaths

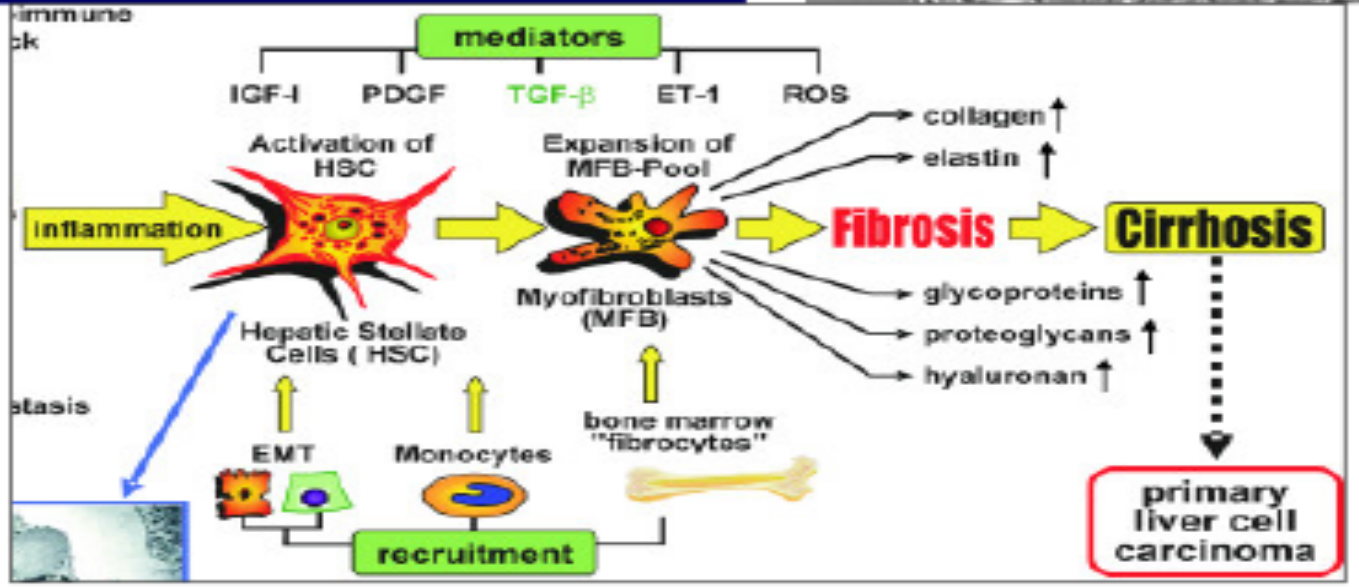


Hepatic stellate cells

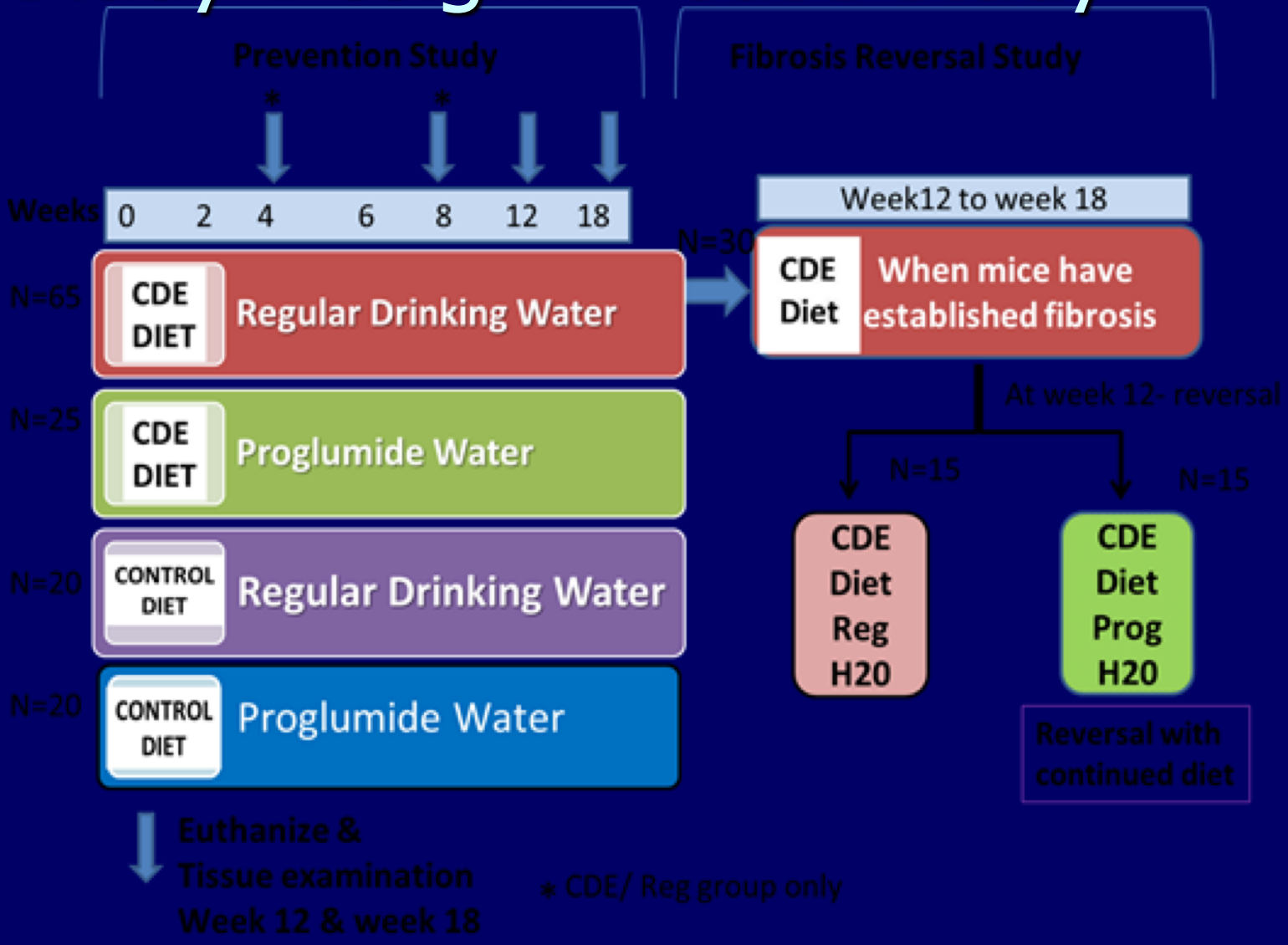




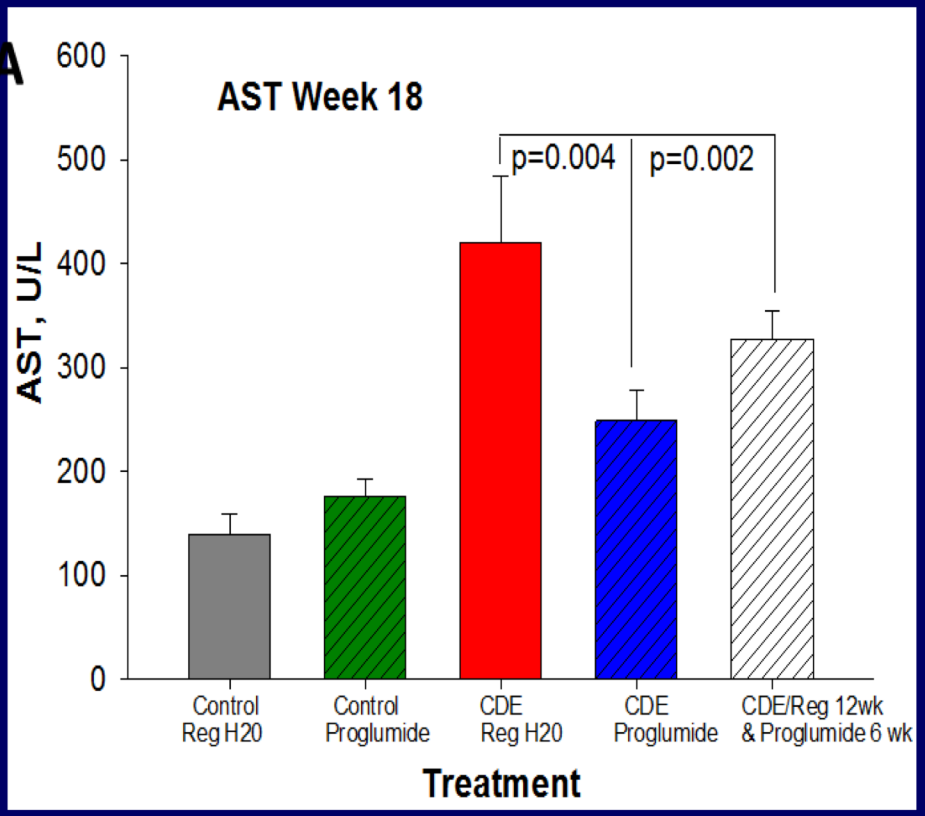
We hypothesized that since pancreatic stellate cells have CCK Receptors that possibly liver stellate cells also have CCK receptors, and that blockade of this receptor could prevent NASH and HCC.

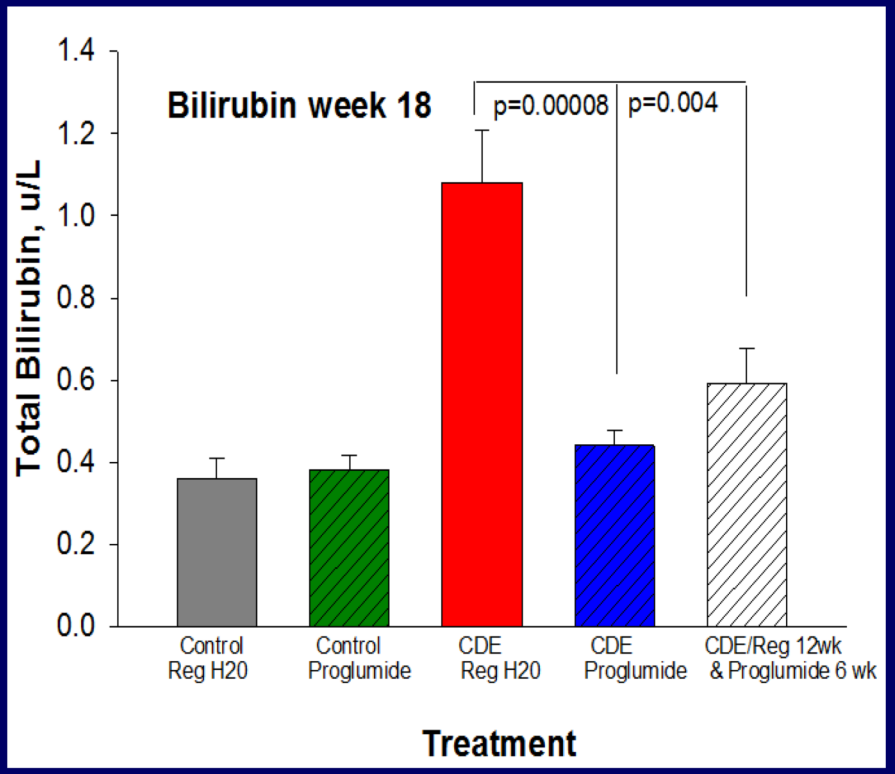


Study Design: Mouse study



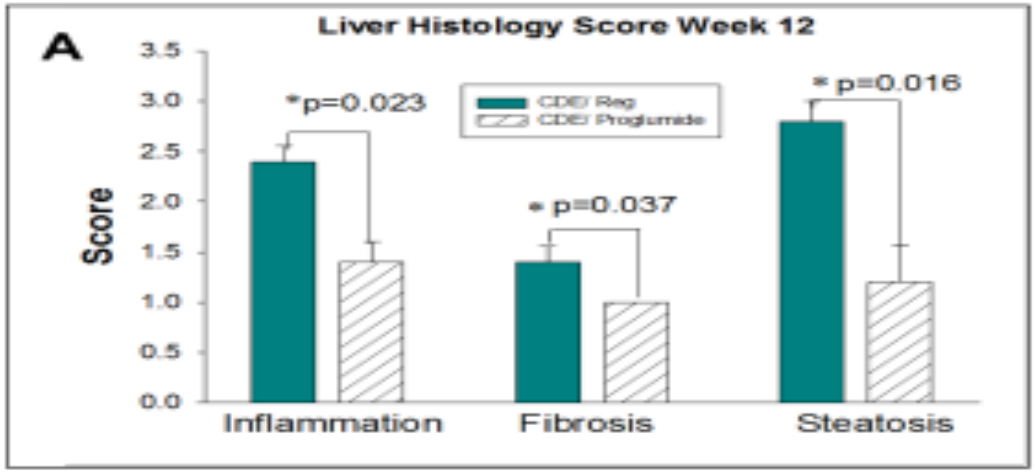
Proglumide lowers liver enzymes

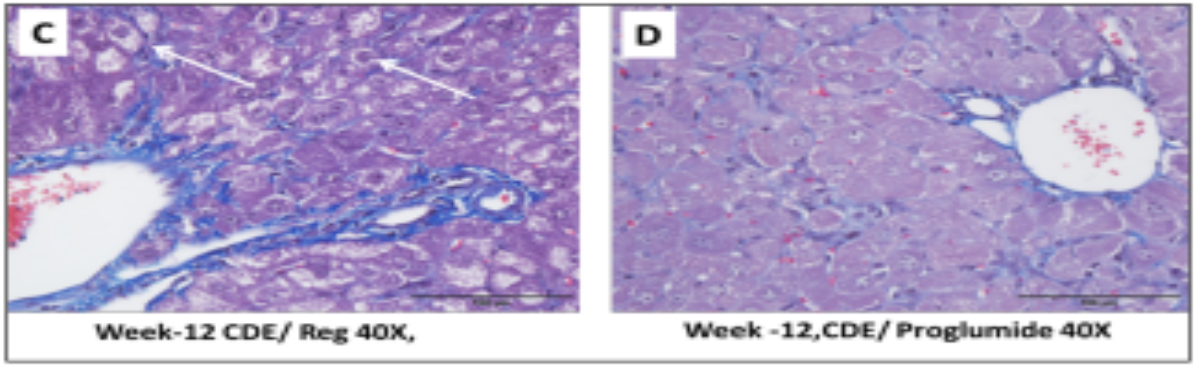




Proglumide reverses NASH

Proglumide Reverses NASH

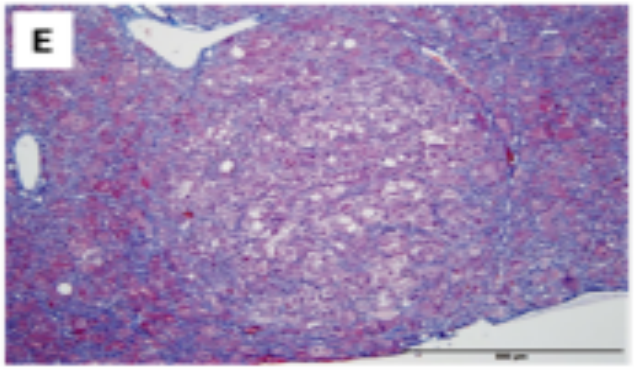




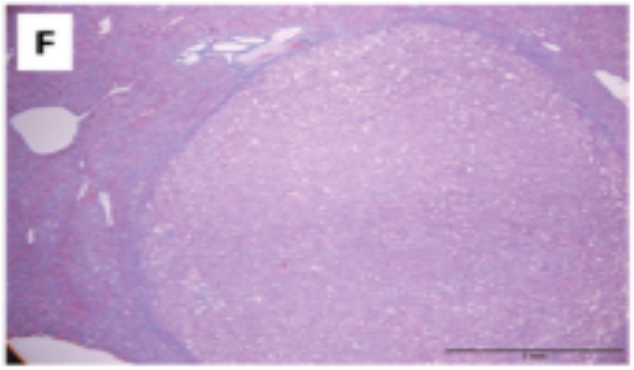
Proglumide and liver cancer

Cancer week 18 CDE/Reg

35% of the mice had HCC at week 18 on the CDE diet.
None of the proglumide treated mice in the prevention or the reversal study had HCC



Week-18, CDE/Reg 10X
Dysplastic Nodule



Week-18, CDE/Reg 4X
Hepatocellular Cancer

Future Clinical Trials

Phase 1 clinical trial NASH **Intellectual property**
IRB approval
FDA IND#
Secured NIH funding from NCI
Publication: Dig Dis Sci. 2019 PMID: 31297627
A Cholecystokinin Receptor Antagonist Halts Nonalcoholic Steatohepatitis
and Prevents Hepatocellular Carcinoma.

Phase 2 trial NASH
Other studies: Conditions with fibrosis such as cirrhosis

Obstacles with Translational Research Today

1. **$$$$$** Is the problem a lack of funds, misuse of funds, or disparity of funds?
2. Clinicians do not get protected time to do translational research.
3. Chiasm between industry and NIH /academia
4. Problems with patient accrual into research studies.
5. No more –one man bands, we need team science. PhDs must work with MDs. Team science

Smith lab

Smith Lab

Funding: NIH / NCI,
Donner Foundation,
Ruesch Foundation